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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,075	02/19/2004	Sean D. Monahan	25772 US2	4417

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EXAMINER
CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
11/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,075	MONAHAN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,10,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,10,13,14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response 06/30/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/10/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 06/30/2009, claims 1, 4-6, 10 and 13-14 are pending in the application.

New Rejections - necessitated by claim amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 10, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are drawn to a "reversibly modified RNA consisting of a hydrophobic group covalently linked to said RNA via a labile bond…". The instant specification describes a modified RNA/lipid complex, modified RNA/polymer complexes and modified RNA/lipid/polymer complexes and describes labile bonds that are cleavable bonds. The specification does not disclose a reversibly modified RNA or define the term for a reversibly modified RNA.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-6, 10, 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "…a hydrophobic group covalently linked to said RNA via a labile bond cleavable under physiological conditions associated through hydrophobic interactions with a transfection reagent to form a complex.". The claim appears to be missing text because it does not state "what" is associated through hydrophobic

interactions. The claims are interpreted to mean the modified RNA associates through hydrophobic interactions with a transfection reagent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 5, 6, 10 and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Fosnaugh et al. (US 2003/0143732 of record PTO Form 892 mailed 12/31/2007) as evidenced by Thierry et al. (US 6,110,490).

The instant claims are drawn to a composition for delivering an RNA to a cell comprising a reversibly modified RNA consisting of a hydrophobic group covalently linked to said RNA via a labile bond cleavable under mammalian physiological conditions associated through hydrophobic interactions with a transfection reagent to form a complex, wherein the hydrophobic group of a membrane active compound, wherein the RNA is modified, selected from siRNA or microRNA, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

Fosnaugh et al. teach conjugates comprising siRNA and functional groups that are used to facilitate delivery of the siRNA into cells (see paragraph 0172). Fosnaugh et al. teach the siRNA can be modified at the 2' hydroxyl position (see paragraph 0165) and teach the functional groups are attached to the siRNA via biodegradable linkers wherein the linkers are degradable in biological systems i.e. mammalian cells (see paragraph 0174). Fosnaugh et al. teach the functional groups can be lipids, peptides, toxins or polymers that are capable of delivering the siRNA across cellular membranes, (see paragraphs 0172- 0175). Moreover, Fosnaugh et al. teach the conjugate can be delivered to an individual using liposomal delivery and teach standard protocols can be used for formation of the liposome complex (see at least paragraph 0195). As evidenced by Thierry et al., liposomal complexes comprising oligonucleotides are formed by hydrophobic interactions (see generally columns 8-11).

Thus Fosnaugh et al. anticipates the instant claims.

Although the foregoing is a new rejection, Applicant's arguments will be addressed as they relate to the prior art cited above. Applicant argues Fosnaugh et al. do not teach a lipid-siRNA combined with a cationic lipid and do not teach siRNA conjugated to a lipid via a labile bond. As stated above Fosnaugh et al. do in fact teach attachment of functional groups such as lipids to siRNA using biodegradable linkers and do teach compositions wherein the siRNA is complexed with cationic liposomes for delivery to individuals.

Claims 1, 5, 6, 10 and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Lewis et al. (US 2003/0143204 of record PTO Form 892 mailed 12/31/2007) and further evidenced by Thierry et al. (US 6,110,490).

The instant claims are drawn to a composition for delivering an RNA to a cell comprising a reversibly modified RNA consisting of a hydrophobic group covalently linked to said RNA via a labile bond cleavable under mammalian physiological conditions associated through hydrophobic interactions with a transfection reagent to form a complex, wherein the hydrophobic group consists of a membrane active compound, wherein the RNA is modified, selected from siRNA or microRNA, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

Lewis et al. teach compositions comprising RNA compounds such as siRNA or antisense wherein the antisense compounds comprise 2'- modifications (see paragraph 0042). Lewis et al. teach the RNA compounds are attached to one or more functional groups used to aid in the delivery of the RNA compound to the cell as well as enhance the stability of the complex wherein such functional groups are cell targeting compounds and hydrophobic groups such as lipids and also carbohydrates (see paragraph 0112). Lewis et al. teach the functional groups are attached via labile bonds that can be selectively broken and dissociated to provide an active inhibitor in the cell (see paragraphs 0120-0141). Lewis et al. teach a complex of siRNA conjugate and a polycation for delivery to cells (see paragraphs 0023-0032). As evidenced by Thierry et

al., liposomal complexes comprising oligonucleotides are formed by hydrophobic interactions (see generally columns 8-11).

Thus Lewis et al. anticipates the instant claims.

Although the foregoing is a new rejection, Applicant's arguments will be addressed as they relate to the prior art cited above. Applicant argues Lewis et al. do not teach the polymers can have labile bonds and do not teach that RNA can be attached to RNA via a labile bond. To the contrary, beginning at paragraph 0120, Lewis et al. discuss the use of labile bonds for attachment of polymers and lipids. do not teach siRNA conjugated to a lipid via a labile bond. Applicants argue Lewis et al. do not teach attaching a hydrophobic group to a siRNA such that the siRNA associates with a transfection agent via hydrophobic interaction. The instant claims are not drawn to attaching of a hydrophobic group that dissociates such that the siRNA associates with a transfection agent. The instant claims are drawn to a composition comprising a RNA covalently linked to a hydrophobic group that is associated through hydrophobic interactions with a transfection reagent to form a complex which as interpreted comprises a siRNA, a hydrophobic group and a transfection reagent such as a cationic liposome.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-6, 10, 13 and 14 rejected under 35 U.S.C. 103(a) as being obvious over Fosnaugh et al. (US 2003/0143732 of record PTO Form 892 mailed 12/31/2007), Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130 of record PTO Form 892 mailed 12/31/2007) and further evidenced by Thierry et al. (US 6,110,490).

The instant claims are drawn to a composition for delivering an RNA to a cell comprising a reversibly modified RNA consisting of a hydrophobic group covalently linked to said RNA via a labile bond cleavable under mammalian physiological conditions associated through hydrophobic interactions with a transfection reagent to form a complex, wherein the hydrophobic group is linked to a ribose 2'-hydroxyl of the RNA and consists of a membrane active compound, wherein the RNA is modified, selected from siRNA or microRNA, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

Fosnaugh et al. teach conjugates comprising siRNA and functional groups that are used to facilitate delivery of the siRNA into cells (see paragraph 0172). Fosnaugh et al. teach the siRNA can be modified at the 2' hydroxyl position (see paragraph 0165) and teach the functional groups are attached to the siRNA via biodegradable linkers wherein the linkers are degradable in biological systems i.e. mammalian cells (see paragraph 0174). Fosnaugh et al. teach the functional groups can be lipids, peptides, toxins or polymers that are capable of delivering the siRNA across cellular membranes,

(see paragraphs 0172- 0175). Moreover, Fosnaugh et al. teach the conjugate can be delivered to an individual using liposomal delivery and teach standard protocols can be used for formation of the liposome complex (see at least paragraph 0195). As evidenced by Thierry et al., liposomal complexes comprising oligonucleotides are formed by hydrophobic interactions (see generally columns 8-11).

Manoharan et al. teach efficient conjugation of conjugates such as carbohydrates and other ligands at the 2' position of the RNA (see page 124).

It would have further been obvious to conjugate functional groups to RNA at the 2' hydroxyl position of the RNA, as taught by Manoharan. Further, one of skill in the art would have been motivated to attach the functional group to the 2' hydroxyl position of a RNA given Manoharan teach this position improves the chemical properties such as stability and nuclease resistance of said RNA molecules. Moreover, one would have expected to conjugate a functional group to the 2' hydroxyl position of a RNA give Manoharan et al. teach efficient RNA molecules with enhanced properties when functional groups are attached at the 2' position.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 4-6, 10, 13 and 14 rejected under 35 U.S.C. 103(a) as being obvious over Lewis et al. (US 2003/0143204 of record PTO Form 892 mailed 12/31/2007),

Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130 of record PTO Form 892 mailed 12/31/2007) and further evidenced by Thierry et al. (US 6,110,490)..

The instant claims are drawn to a composition for delivering an RNA to a cell comprising a reversibly modified RNA consisting of a hydrophobic group covalently linked to said RNA via a labile bond cleavable under mammalian physiological conditions associated through hydrophobic interactions with a transfection reagent to form a complex, wherein the hydrophobic group is linked to a ribose 2'-hydroxyl of the RNA and consists of a membrane active compound, wherein the RNA is modified, selected from siRNA or microRNA, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

Lewis et al. teach compositions comprising RNA compounds such as siRNA or antisense wherein the antisense compounds comprise 2'- modifications (see paragraph 0042). Lewis et al. teach the RNA compounds are attached to functional groups used to aid in the delivery of the RNA compound to the cell as well as enhance the stability of the complex and teach when attached to functional groups, the functional group alters the interactions of the complex to the attached group and teach such functional groups are cell targeting compounds and hydrophobic groups such as lipids and also carbohydrates (see paragraph 0112). Lewis et al. further teach multiple functional groups can be attached (see paragraph 0032). Lewis et al. teach the functional groups are attached via labile bonds that can be selectively broken and dissociated to provide an active inhibitor in the cell (see paragraphs 0120-0128). Lewis et al. do not

specifically teach attachment of the functional groups such as lipids at the 2' position of the ribose nor teach the modified siRNA comprising silylated, acylated or alkylated RNA.

Manoharan et al. teach efficient conjugation of conjugates such as carbohydrates and other ligands at the 2' position of the RNA (see page 124).

It would have been obvious to conjugate functional groups to RNA at the 2' hydroxyl position of the RNA, as taught by Manoharan. Further, one of skill in the art would have wanted to attach the functional group to the 2' hydroxyl position of a RNA given Manoharan teach this position improves the chemical properties such as stability and nuclease resistance of said RNA molecules. One would have expected to conjugate a functional group to the 2' hydroxyl position of a RNA give Manoharan et al. teach efficient RNA molecules with enhanced properties when functional groups are attached at the 2' position.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Claim Rejections - 35 USC § 112 - withdrawn

The rejection of claims 1, 4-6, 10 and 13-14 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

Claim Rejections - 35 USC § 103 - withdrawn

The rejection of claims 1, 4-6, 10, 13 and 14 under 35 U.S.C. 103(a) as being obvious over Fosnaugh et al. (US 2003/0143732), Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130) and Goldsborough (of record PTO Form 892 11/29/2005) is withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Tracy Vivlemore at 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
Primary Examiner
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